ABC Multidrug Transporters: Target for Modulation of Drug Pharmacokinetics and Drug-Drug Interactions

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Abstract: Nine proteins of the ABC superfamily (P-glycoprotein, 7 MRPs and BCRP) are involved in multidrug transport. Being localised at the surface of endothelial or epithelial cells, they expel drugs back to the external medium (if located at the apical side [P-glycoprotein, BCRP, MRP2, MRP4 in the kidney]) or to the blood (if located at the basolateral side [MRP1, MRP3, MRP4, MRP5]), modulating thereby their absorption, distribution, and elimination. In the CNS, most transporters are oriented to expel drugs to the blood. Transporters also cooperate with Phase I/Phase II metabolism enzymes by eliminating drug metabolites. Their major features are (i) their capacity to recognize drugs belonging to unrelated pharmacological classes, and (ii) their redundancy, a single molecule being possibly substrate for different transporters. This ensures an efficient protection of the body against invasion by xenobiotics. Competition for transport is now characterized as a mechanism of interaction between co-administered drugs, one molecule limiting the transport of the other, which potentially affects bioavailability, distribution, and/or elimination. Again, this mechanism reinforces drug interactions mediated by cytochrome P450 inhibition, as many substrates of P-glycoprotein and CYP3A4 are common. Induction of the expression of genes coding for MDR transporters is another mechanism of drug interaction, which could affect all drug substrates of the up-regulated transporter. Overexpression of MDR transporters confers resistance to anticancer agents and other therapies. All together, these data justify why studying drug active transport should be part of the evaluation of new drugs, as recently recommended by the FDA.

Keywords: P-glycoprotein**,** BCRP, MRP, ADME properties, drug-drug interactions.

INTRODUCTION

The proteins from the ATP-binding cassette (ABC) transporters superfamily share as common features a capacity to actively transport molecules through the membranes, and to use ATP hydrolysis as an energy source. They have been classified in seven subfamilies (ABCA to ABCG), according mainly to sequence homologies and structural organization [1]. The topology and nomenclature of ABC transporters have been extensively reviewed elsewhere [2-4] and will not be addressed here.

Most of the 48 human ABC transporters (without the truncated ABCC13 with still unknown function [5]) play a role in the export of physiological substrates (amino acids, peptides, lipids, inorganic ions…), but nine of them are rather associated to a Multi-Drug Resistance (MDR) phenotype, due to their ability to extrude out of the cells a large variety of xenobiotics.[1] These are the P-glycoprotein (ABCB1, P-gp), the Multidrug Resistance associated Proteins or MRPs (MRP1-MRP7, also referred to as ABCC1-6 and ABCC10), and the Breast Cancer Resistance Protein or BCRP (ABCG2). In addition, the intracellular transporter ABCA3 has also been implicated in multidrug resistance in leukemia cells, as it can sequester drugs inside lysosomes [8]. The role of these MDR transporters, and of P-gp in particular, is well described in the context of resistance to anticancer drugs [9, 10]. Yet, as they are widely distributed in the organism [11], they also play an important role in the modulation of absorption, tissue distribution and elimination of their substrates or in the protection of sanctuaries, like the central nervous system (Fig. **1**). MDR ABC transporters are therefore considered as a major intervenient in the pharmacokinetics of many drugs, which can in its turn modulate their pharmacological activity or their toxicity [12-14]. A first goal of this paper is to review the current knowledge on the role of MDR ABC transporters in drug transport and its consequences in terms of ADME properties.

A striking characteristic of these MDR transporters is the wide variety of apparently non chemically-related substrates they can accommodate. This is not yet fully understood, but the structure of the murine P-gp (Abcb1a) recently resolved at a 3.8 Å resolution [15], together with the structural models of different MDR ABC established by homology modeling using crystallographic structures from bacterial homologs [16-22], may be helpful in this respect. A pharmacological consequence of this broad substrate specificity is that co-administration of drug substrates may cause drug-drug interactions by competition for a same transporter. Moreover, drugs can also induce the expression of transporters, modifying thereby their capacity to transport their substrates [13]. A second goal of this paper is to examine how these recently described mechanisms of drug-drug interactions can affect drug pharmacokinetic properties.

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[1] Transporters involved in drug influx belong to another superfamily of transporters, namely the SLC (Solute-Linked Carrier) family (a family of secondary transporters that comprises the organic anion transporting polypeptides (OATPs), the organic anion transporters (OATs) or the organic cation transporters (OCTs)). These also play an important role in drug pharmacokinetics and drug-drug interactions [6, 7] but will not be discussed here.

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PHYSIOLOGICAL FUNCTIONS OF MDR ABC TRANSPORTERS

Table **1** illustrates the localization, expression levels (at the mRNA or protein level), and physiological substrates of MDR ABC transporters. Caution is required however when data refers only to mRNA levels, as discrepancies between mRNA and protein levels may exist. For example, BCRP expression in kidney is low at mRNA level but higher at protein level [23]. Moreover, spliced mRNA variants do not always code for an entire, functional protein [24-27]. While some of these transporters, like P-gp, have a very broad tissue distribution, others are expressed only in a few organs, like MRP7. For the latter, this suggests specific roles in these organs, even though these have rarely been evidenced. Considering MRP7, for example, it is interesting to note that it is expressed in the heart and can transport leukotriene C4, a well known vasoconstrictor agent [28]. Likewise, MRP4 is highly expressed in prostate and expels cyclic nucleotides that control erectile function and smooth muscle activity in the urinary tract [29]. The expression level of a given transporter can also markedly vary from one organ to the other, depending of its specific role. P-gp for example is highly expressed at the apical membrane of many epithelial cells (enterocytes, renal tubules, canalicular membrane of hepatocytes) or brain capillary endothelium [11], in relation with its detoxification function. More intriguingly, some transporters can be found either at the apical or at the basolateral membrane, depending on the tissue. This is mostly the case for MRP4, which is usually located at the basolateral membrane but is found at the apical surface of renal epithelial cells and brain endothelial cells (for a review, refer to [30]). The basolateral transporters MRP1 and MRP5 have also been detected at the apical membrane of brain endothelial cells [31], although at low levels. This may contribute to reinforce the protective effect of P-gp or BCRP on the brain.

MDR TRANSPORTERS AND MODULATION OF DRUG PHARMACOKINETICS

Fig. (**1**) illustrates the main role of MDR ABC transporters with respect to drug disposition in the organism. Those that are localized at the apical surface of the cells bordering the elimination organs will contribute to cell detoxification by expelling xenobiotics into the bile, the urine or the faeces; those that are expressed at the basolateral surface will rather contribute to drug (re)absorption by driving them from the intracellular medium to the blood [30, 32]. MRPs mainly transport Phase II metabolites (drug conjugates to glutathione, glucuronate or sulfate [33]) and constitute therefore the "Phase III" of drug elimination [34, 35].

At the level of barriers separating the blood from sanctuaries or vulnerable organs like the brain, the placenta or the testis, most transporters are oriented towards a transport from the organ to the blood, as a way to protect these fragile sites from foreign invasion [36, 37]. This role is best evidenced by the specific neurotoxicity of ivermectin in beagle dogs that are naturally deficient in P-glycoprotein [38]. In non-polarized cells, efflux pumps can contribute to reduce the cellular concentration of drugs and hence, their pharmacological activity if they act upon an intracellular target. This is well exemplified by the reduction in intracellular activity of fluoroquinolones, macrolides, or daptomycin against bacteria infecting macrophages expressing MDR transporters [39, 40] or of anti-HIV drugs in infected macrophages and lymphocytes [41]. *A fortiori*, overexpression of MDR transporters is a well established mechanism of resistance of cancer cells to chemotherapy [10, 42, 43].

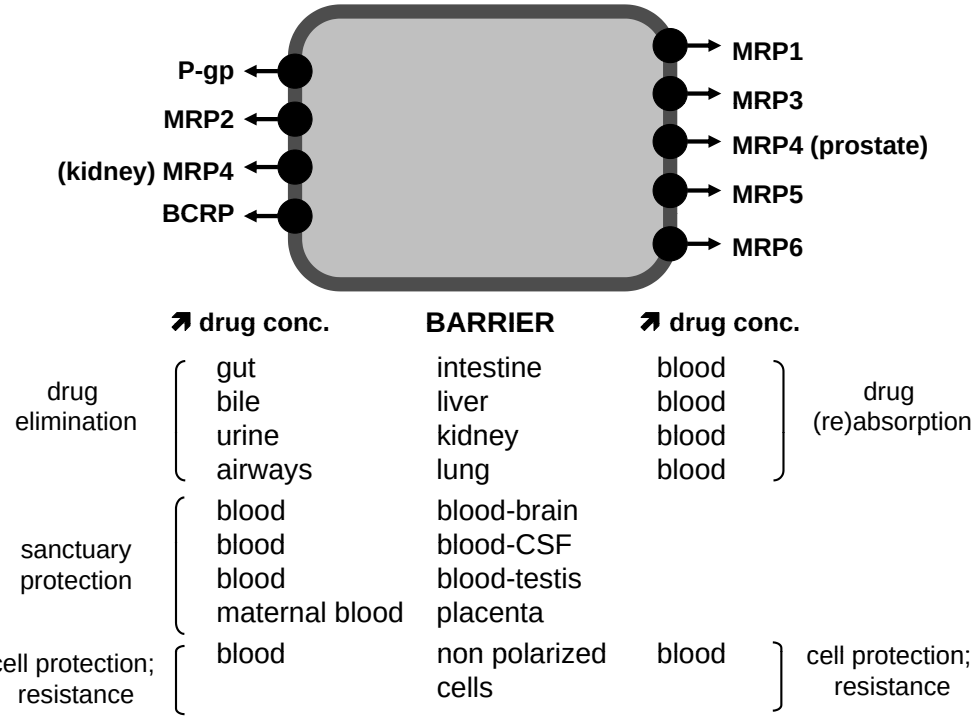

Fig. (1). Illustration of the role of MDR ABC transporters in the modulation of drug disposition when expressed at the apical or basolateral side of the cells bordering the main barriers in the body, or in non polarized cells.

Table 1. Localization and Physiological Substrates of ABC Transporters

ABC Transporter	Localization	Tissue Distribution		Physiological Substrates	Refs.
		High Expression	Low Expression		
P-gp (ABCB1)	Apical	Kidney, adrenal gland, liver, pancreas, intestine, lung, blood-brain barrier, placenta	Prostate, skin, heart, skeletal muscle, ovary	Phospholipids, cytokines, steroids	[11, 220]
MRP1 (ABCC1)	Basolateral (except in placenta and BBB)	Kidney, lung, testis, skeletal and cardiac muscles, placenta (apical)	Liver, intestine, brain	Glutathione, glutathione conjugates (LTC4, DNP-SG), bilirubin glucuronides, bile salts	[31, 221-223]
MRP2 (ABCC2)	Apical	Liver, kidney, small intestine, placenta		LTC4, DNP-SG, bilirubin glucuronides, sulphated bile salts	[183, 222, 224, 225]
MRP3 (ABCC3)	Basolateral	Adrenal gland, intestine, pancreas, gallbladder, placenta	Liver, kidney, prostate*	Bile salts, LTC4, estradiol-17β-glucuronide, bilirubin-glucuronides	[222, 226, 227]
MRP4 (ABCC4)	Apical (kidney, BBB) or basolateral (prostate, choroid plexus)	Prostate	Ovary*, testis*, kidney, lung*, intestine*, liver, brain, pancreas	cAMP, cGMP, bile salts, folate, conjugated steroids, prostaglandins (PGE1, PGE2)	[31, 228-232]
MRP5 (ABCC5)	Basolateral (except in BBB)	Skeletal* and cardiac muscle, testis*	Brain, neurons, liver*	cAMP, cGMP, folate, DNP-SG	[31, 227]
MRP6 (ABCC6)	Basolateral	Liver, kidney, skin, lung, heart, intestine, pancreas, stomach		LTC4, DNP-SG	[233, 234]
MRP7 (ABCC10)	?		Colon*, skin*, testis*, pancreas*	Estradiol-17β-glucuronide, LTC4	[235, 236]
BCRP (ABCG2)	Apical	Placenta, breast, blood-brain barrier, liver, intestine,	Kidney, lung, ovary*, testis* pancreas*	Vitamins (riboflavin, biotin), porphyrins, estrogen sulfate conjugates	[23, 237-240]

BBB, blood-brain barrier; LTC4, leukotriene C4; DNP-SG, 2,4-dinitrophenyl-*S*-glutathione.
*Data for gene expression only (mRNA); otherwise, the tissue distribution refers to protein detection.

Table 2. Pharmacologically Relevant Substrates of MDR ABC Transporters

ATC Code		Pharmacological Class	Drug	P-gp	MRP1	MRP2	MRP3	MRP4	MRP5	MRP6	MRP7	BCRP	Refs.
Alimentary tract and metabolism													
A	02B	H2-receptor antagonists	Cimetidine	+								+	[241, 242]
			Nizatidine	+									[243]
			Ranitidine	+									[242]
	03F	Propulsives	Domperidone	+									[101]
	04A	Antiemetics	Ondansetron	+									[101]
	07D	Antipropulsives	Loperamide	+									[101]
Cardiovascular system													
C	01A	Cardiac glycosides	Digoxin	+*								-*	[100, 241]
			Talinolol	+ (r)									[244]
	01B	Anti-arrhythmics	Quinidine	+ (r)*									
	02C	Antihypertensives	Prazosin	+ (m)								+ (m)	[245]
	07A	Beta-blocking agents	Celiprolol	+									[246]
	08C	Calcium channel blockers (vascular)	Nicardipine	*								+	[247, 248]
			Nifedipine	+(r)*								+	[247, 249]
	08D	Calcium channel blockers (cardiac)	Diltiazem	+*									[250]
			Verapamil	+*									[251]
	09C	Angiotensin II antagonists	Losartan	+	-	-							[252]

(Table 2) Contd…..

ATC Code		Pharmacological Class	Drug	P-gp	MRP1	MRP2	MRP3	MRP4	MRP5	MRP6	MRP7	BCRP	Refs.
C	10A	Lipid modifying agents	Ezetimibe	+		+							[253]
			Atorvastatin	+*									[254-256]
			Pitavastatin	+		+						+	[257]
			Pravastatin			+ (r)		+					[258, 259]
			Rosuvastatin	+		+						+	[260, 261]
Systemic hormons													
H	02A	Corticosteroids	Dexamethasone	+								-*	[100, 241]
Anti-infectives													
J	01A	Tetracyclines	Tetracycline	+				+					[258, 262]
	01C	Beta-lactams[a]		+		+		+				+ (r)	[258, 263-265]
	01F	Macrolides[a]		+	+	+ (r)							[266-268]
		Ketolides	Telithromycin	+		+ (r)							[269]
	01M	Fluoroquinolones[a]		+	+	+ (r)		+ (m)				+	[58, 268, 270-276]
	01X	Nitrofuranes	Nitrofurantoin									+	[277]
		Lipopeptides	Daptomycin	+									[40]
	02A	Azole antifungals	Itraconazole	+ (m)								-*	[164, 278]
	04A	Antimycobacterial antibiotics	Rifampicin	+ (m)									[279]
	05A	Reverse transcriptase inhibitors	Adefovir	- (CHO)	-			+	+		+	+ (m)	[44, 228, 280-283]
			Ganciclovir					+					[284]
			Zidovudine (AZT)					+				+	[282, 285]
		Protease inhibitors	Indinavir	+	+/-	+	-		-			-	[89, 162, 286-288]
			Lopinavir	+	-	+						- (m)	[289]
			Nelfinavir	+	+							-*	[89, 162, 288]
			Ritonavir	+	+/-	+	-		-			-*	[162, 286-288]
			Saquinavir	+	+/-	+	-		-			-*	[89, 162, 286-288, 290]
Antineoplastic and immunomodulating agents													
L	01B	Antimetabolites	Cladribine					+				+	[44, 291]
			Methotrexate	+	+	+	+	+	+			+[b] (and PG)	[292-299]
	01C	Plant alkaloids	Docetaxel	+		+					+		[300-302]
			Paclitaxel	+	-	+	-	-			+	-	[62, 228, 295, 300, 301, 303-305]
			Etoposide	+	+/-	+ (GC)	+ (and GC)	-		+	+	-	[62, 228, 281, 295, 304, 306-310]
			Vinblastine	+	+	+[#]		-			+		[228, 301, 304, 311-313]
			Vincristine	+	+[#]	+[#]	+/-	-			+		[228, 295, 301, 303, 307, 310, 314, 315]

(Table 2) Contd…..

ATC Code		Pharmacological Class	Drug	P-gp	MRP1	MRP2	MRP3	MRP4	MRP5	MRP6	MRP7	BCRP	Refs.
L	01D	Cytotoxic antibiotics	Actinomycin D	+	+								[304, 314]
			Daunorubicin	+	+ (GS)		-	-		+	+	+[b]	[62, 228, 281, 295, 303, 304, 308, 314, 316, 317]
			Doxorubicin	+	+ (GS)	+	-	-		+		+[b]	[62, 228, 295, 303, 304, 307, 308, 310, 316-318]
			Mitoxantrone	+	+[#]							+[b]	[62, 316, 319, 320]
	01X	Camptothecins	Irinotecan	+	+	+		+				+	[321-324]
			Topotecan	+				+				+	[325-328]
	-		Gimatecan	-		-		+				-	[329]
	-	Platinium compounds	Cisplatin			+[#]	-						[307, 310, 330]
	-	Protein kinase inhibitors	Imatinib	+								+/-*	[331-334]
			Lapatinib	+								+	[335]
	-	-	Becatecarin									+	[336]
	-	-	Flavopiridol	+ (m) /-	-							+/-	[62, 245, 337]
	04A	Immunosuppressants	Ciclosporin A	+*				-				-*	[100, 155, 324, 338]
			Tacrolimus	+								-*	[155, 338]
Musculo-skeletal system													
M	01A	Anti-inflammatory agents	Diclofenac	-		-						+	[142]
	04A	Antigout agents	Colchicine	+		+						-	[339]
Brain and nervous system													
N	02A	Opioid analgesics	Morphine	+ (CHO)		+ (GC)	+ (GC) (m)					-	[340-342]
			Oxycodone	+									[200]
	-	Analgesics	Asimadoline	+									[105]
	03A	Antiepileptics	Phenobarbital	+	-	-			-				[343, 344]
			Phenytoin	+	-	-			-			-	[343-345]
			Topiramate	+	-	-			-				[346]
	04B	Antiparkinsonian drugs	Bromocriptine	+ (m)									[347]
			Budipine	+ (m)									[348]
			L-dopa	+									[349]
	05A	Antipsychotic drugs	Fluphenazine	+									[350]
			Perazine	+									[350]
			Risperidone	+									[351]
	06A	Antidepressants	Citalopram	+ (m)									[352]
			Trimipramine	+ (m)									[352]
Antiparasitic products													
P	01B	Antiparasitics	Chloroquine	-	+								[353, 354]
			Mefloquine		+			+					[355]
			Quinine	+									[353]
	-		Quinacrine	+ (m)									[356]
	02C	Antihelmintics	Ivermectin	+									[100]
	-		Oxfendazole	-		-						+	[357]

(Table 2) Contd…..

ATC Code		Pharmacological Class	Drug	P-gp	MRP1	MRP2	MRP3	MRP4	MRP5	MRP6	MRP7	BCRP	Refs.
Respiratory system													
R	06A	Antihistaminics	Cetirizine	+	+								[358]
			Fexofenadine	+		+							[359, 360]
Various													
V	03A	Antidotes (morphinic antagonist)	Methadone	+								-	[341, 361]

Drug are classified according to ATC codes (Anatomical Therapeutic Chemical classification system; http://www.whocc.no/atc/).
All data refer to studies with human transporters, except when specifically indicated: (m) mouse; (r) rat; (CHO) Chinese hamster ovary cells.
Key: +, substrate; -, non substrate; *, modulator/inhibitor [143]; #, transport is dependent upon the presence of glutathione; GS, glutathione conjugate; GC, glucuronide conjugate; PG, polyglutamate conjugate.
[a], does not apply to the whole class (some members are substrates, others, not); [b], BCRP substrate specificity is affected by mutations at amino acid 482 [62].

Table **2** summarizes our current knowledge on the active transport of drugs by the main MDR ABC transporters. A first observation is that a single transporter can affect a very large number of molecules, belonging to a wide variety of pharmacological classes and presenting markedly remote chemical structures. P-gp substrates are mostly organic amphipathic molecules, ranging in size from less than 200 Da to almost 1900 Da. Most of them are neutral or basic compounds, but zwitterionic and negatively charged compounds (like methotrexate) can also be transported. Among MRPs, MRP4 and MRP5 have the particularity to transport cyclic nucleotides and purine analogues [44-46], but not anthracyclines, taxanes, or vinca alkaloids. BCRP shows a broad substrate specificity, with partial overlap with P-gp substrates. On the other hand, all drugs belonging to a same pharmacological class are not necessarily substrates for the same transporter. All together, these data suggest that recognition by MDR transporters depends on molecular determinants that have nothing in common with those defining the high specificity of drug-target interaction in most pharmacological models (classical model of the key-and-lock recognition [47]). Yet, converging evidence from experimental studies and molecular modeling tend to indicate that these are the global physico-chemical properties of the molecule rather than the presence of specific substituents that drive substrate recognition. Tentative 'pharmacophores' have been progressively built up that allow to predict possible interactions, mainly with P-glycoprotein, and are now used for *in silico* screening [48, 49]. The features identified include the presence of hydrogen bond acceptor, hydrophobic and aromatic areas, and positive ionizable group at appropriate distance from one another [50]. Another factor that can contribute to broad substrate specificity is the fact that MDR transporters possess several binding sites in the transmembrane domains, as demonstrated for P-gp [51-53], MRP2 [54] or BCRP [55], which can probably accommodate different substrates [56].

A second observation is that a single molecule can be substrate for different transporters. At the molecular level, this indicates that common features may dictate recognition by different transporters. In this respect, it is interesting to note that this may even apply to totally unrelated transporters, as those conferring resistance to antibiotics in bacteria. For example, ciprofloxacin but not moxifloxacin, is substrate of murine Mrp4 [57, 58] as well as of efflux pumps conferring resistance to fluoroquinolones in *Staphylococcus aureus*, *Streptococcus pneumoniae,* or *Listeria monocytogenes* [59-61]. At the physiological level, this redundancy between transporters may compensate for the poor expression of a given transporter in a particular tissue and/or for alteration of activity in mutated proteins. Mutagenesis studies have indeed shown that substrate specificity can be affected by a single amino acid change (see for example [62] for BCRP or [63] for P-glycoprotein). Indeed, *in vivo* also, variations in ABC transporters expression between individuals is well documented [64, 65], as well as genetic polymorphisms (see for review [66] for P-gp and MRP2 and [67] for BCRP). These polymorphisms might however be clinically relevant only at certain drug doses.

A third observation is that P-glycoprotein seems by far to be the broadest spectrum transporter. This conclusion needs however to be taken with caution, as P-glycoprotein is also the most widely studied transporter. Empty cells in Table **2** need thus to be interpreted as an absence of data and not necessarily as an absence of transport. Other possible limitations of the data presented in this Table are that some of them have been performed in animal cells (exploring therefore transport capacity of the animal transporter), or in animal cells transfected with human transporter (but with the remaining background of the other transporters expressed by the animal cell) or using knockout animals. Transposition of the results to human needs therefore careful appreciation due to interspecies substrate discrepancies. Thus, whereas mouse Bcrp1 was functionally comparable with human BCRP in a murine fibroblast cell line [68], interspecies differences do exist between Bcrp1/BCRP in hepatocytes [69], as well as between murine and human MRP2/Mrp2 [70, 71], or P-gp [72, 73].

Consequences for Drug Absorption (Intestinal Barrier)

Drugs administrated by oral route must pass through several barriers before reaching their target site, the first one being the intestinal epithelium. Due to their high expression in the small intestine and to their co-localization at the apical membrane of enterocytes, P-gp, MRP2, and BCRP play a key role in limiting the absorption of drugs by expelling them back to the intestinal lumen [74, 75]. Expression of transporters along the small intestine is not uniform and regional differences have been reported (see for review [75]): whereas P-gp expression is higher in the ileum [76], MRP2 and BCRP expression are higher in jejunum [77, 78]. This will affect locally drug absorption at the intestinal

barrier. For example, a significant inverse correlation was found between ciclosporin A absorption and intestinal P-gp mRNA levels along the gastrointestinal tract [79].

To date, the role of P-gp is the most documented [80]. In the mice, however, Bcrp1 has been shown to limit the oral bioavailability of the anticancer drug topotecan [81], and to protect the animals against ingested dietary carcinogens (such as 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, PhIP) [82] or phototoxins like pheophorbide A [83]. On the contrary, MRP transporters expressed at the basolateral side of the cells may increase drug absorption. This has been demonstrated for ampicillin [84] or adefovir [85] using *in vitro* models of intestinal barrier.

The tools developed to study the role of P-gp in intestinal drug absorption consist of *in vitro* models of Caco-2 cell monolayers [86] and *in vivo* models with knockout mice [87]. Mice express two isoforms of P-gp, namely Mdr1a and Mdr1b, which both act as multidrug transporters; however, Mdr1b is not detected in the intestine. *Mdr1a* (-/-) mice allowed for example to demonstrate the major role of P-gp in the pharmacokinetics of paclitaxel [88] or HIV protease inhibitors (indinavir, nelfinavir and saquinavir [89]), since drug plasmatic concentrations were significantly higher in *Mdr1a* (-/-) mice than in WT mice (6-fold higher for paclitaxel, and 2- to 5-fold higher for HIV protease inhibitors). Studies with healthy volunteers allowed to confirm the importance of P-gp expression levels [79] or of the co-administration of pump inhibitors for drug absorption [90].

Moreover, detoxifying enzymes of cytochrome P450 family are likely to act in synergy with ABC transporters to decrease drug absorption [91, 92]. Cytochrome P450 3A4 (CYP3A4) accounts for nearly 70% of all CYP enzymes expressed in small intestine [93]. It displays a substantial overlap in substrate specificity and colocalizes with P-gp in enterocytes [94]. Recently developed models of *Mdr1a/1b* (-/-), *Cyp3a* (-/-), and *Cyp3a/Mdr1a/1b* (-/-) mice will thus be of prime interest to evaluate the respective importance of metabolism and efflux in drug disposition. Of high interest, recent data obtained with this model suggest that there is a high degree of synergy between Cyp3a and Mdr1a. For example, a >70-fold increase in systemic exposure to docetaxel is observed after oral administration to *Cyp3a/Mdr1a/1b* (-/-) mice *vs.* a 12-fold increase in *Cyp3a* (-/-) mice and a 3-fold increase in *Mdr1a/1b* (-/-) mice [95]. Mathematical models have been developed to predict the change in AUC mediated by each of these systems for drugs that are common substrates [96]. Yet, the observation of synergistic effects makes probably largely pointless evaluations of the individual contribution of each of these mechanisms with respect to modifications of drug bioavailability *in vivo.*

Consequences for Drug Distribution

ABC transporters located at the blood-brain barrier (BBB), the blood-CSF barrier, the blood-placental barrier, or the blood-testis barrier restrict the penetration of xenobiotics into the central nervous system, the foetus (via the placenta) or the testis. While this contributes to protect these vulnerable territories, it also compromises drug accessibility in pathological situations. This is most conspicuously the case for central nervous diseases (neurodegenerative diseases, intracranial tumors, dementia, epilepsy, meningitis…). Two physiological barriers separate the brain from the bloodstream. The blood-brain barrier (BBB) is made of endothelial cells of the brain microvasculature that isolate the cerebral blood from the brain interstitial fluid. Tight junctions between these cells limit the paracellular flux of hydrophilic molecules across the BBB, so that only lipophilic molecules with low molecular weight can passively diffuse. The blood-cerebrospinal fluid (CSF) barrier is formed by a single layer of choroid plexus epithelial cells that separates the plexus blood from the CSF. BCRP and P-gp are the main ABC transporters expressed at the human BBB [97]; they are both localized at the apical (or luminal) pole of the BBB where they transport drugs from the brain to the blood. MRPs are also detected but with a lower expression; their functional role at the BBB still needs to be clearly determined [98].

The first studies investigating the influence of ABC transporters at the BBB were performed *in vitro*, using cultures of brain endothelial cells. These cells however do not always exhibit all the properties of *in situ* brain microvessel endothelial cells [98]. P-gp-knockout mice models were thereafter used to demonstrate the implication of P-gp to limit drugs entry into the brain, Mdr1a being the major P-gp isoform present at the BBB. The first studies with *Mdr1a* (-/-) mice showed that they were almost 100-fold more sensitive to the neurotoxic effects of ivermectin, an antiparasitic compound [87] than wild-type mice. Many other P-gp substrates, such as digoxin [99, 100], ciclosporin A [100], loperamide, domperidone and ondansetron [101], HIV protease inhibitors (indinavir, saquinavir, nelfinavir) [89], or paclitaxel [102] are accumulated in the brains of P-gp-deficient mice up to 35- or 40-fold higher than in WT mice, clearly documenting the role of P-gp as a gatekeeper at the luminal side of the BBB [103]. Several studies also evidenced a more marked implication of Mdr1a at the BBB than at the intestinal barrier by comparing the increase in drug concentration in the brain *vs*. the intestine of *Mdr1a* (-/-) or *Mdr1a/1b* (-/-) mice as compared to wild-type animals (4.4- to 9.6-fold *vs*. 2-fold for vinblastine [104]; 9-fold *vs*. no effect for asimadoline, an experimental analgesic [105]). More recently, positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging techniques [106] with radiolabeled efflux pump substrates have allowed non-invasive studies in animals and humans and a direct visualization of drug transporter function at the BBB [107, 108].

Although expressed at the BBB [109], Bcrp1 seems to have a moderate role in the transport of substances known to be BCRP substrates, such as imatinib [110] and mitoxantrone [111], or of xenobiotics that are also P-gp substrates [112, 113]. Yet, other studies showed the Bcrp1 acts synergistically with P-gp to limit the brain penetration of topotecan [114] and lapatinib [115]. In case of P-gp deficiency, however, Bcrp1 expression at the BBB increases, which is accompanied by greater export of its substrates, like mitoxantrone or prazosin [116]. Mrp4 presents the particularity of being expressed at the apical membrane of endothelial cells at the BBB but at the basolateral membrane of epithelial cells at the blood-CSF barrier. This dual localization allows for clearance of Mrp4 substrates from both the CSF

and the brain, as shown for topotecan [117]. However, this effect has been observed in rodents and might not be relevant in humans, where MRP4 expression seems to be very low [118].

In the placenta, P-gp expressed in trophoblasts protects the fetus from potential teratogenic compounds [119], and from many drugs like digoxin, saquinavir or paclitaxel [120] extruding them into the maternal blood. Likewise, Bcrp1, expressed in placental syncytiotrophoblasts [109], limits the foetal penetration of topotecan [81]. Again the role of active transporters as a limitation to the permeability of the foeto-maternal barrier may rationalize clinical observations, for example the lack of efficacy of protease inhibitors for preventing HIV transmission in pregnant women [121].

Consequences for Drug Elimination

A role for intestinal P-gp in the elimination of drugs from the blood to the gut lumen has been described [122], but the main routes of drug elimination remain through biliary excretion and renal clearance.

Biliary Excretion of Drugs

In the liver, a lot of transporters are involved not only in the excretion of bile constituents, but also of xenobiotics and metabolites produced by Phase I and Phase II enzymes. These include MDR transporters, but also other ABC transporters like BSEP (Bile Salt Export Pump, ABCB11) and Solute-Linked Carrier transporters [123, 124]. P-gp, MRP2 and BCRP are localized at the canicular membrane of hepatocytes and secrete metabolized xenobiotics into the bile. MRP1, MRP3 and MRP4 are expressed at the basolateral membrane and extrude metabolites in the blood, from where they can be eliminated by the kidneys (for a review, see [125]). Hepatic cells appear thus as a hub, orientating the route of elimination of metabolized drugs depending on their affinity for apical or basolateral transporters.

Transporters can also cooperate at the level of different barriers to efficiently reduce drug concentrations in the blood. For example, a complementary role of P-gp and Mrps has been evidenced for paclitaxel [126] and etoposide [127]. While P-gp is mainly involved in restricting their intestinal absorption, Mrp2 dominates in their hepatobiliary excretion. Moreover, in Mrp2 deficient animals (Mrp2 knockout mice), Mrp3 can secrete etoposide metabolites from the liver to the blood, from where they are further eliminated in urine [127]. Thus, MRP3 is considered to function as a backup detoxifying pathway for hepatocytes, since its expression is increased when the normal canicular route is damaged by cholestatic diseases or when the function of MRP2 is impaired [128].

Renal Drug Excretion

In renal epithelial cells, P-gp, MRP2, and MRP4 are expressed at the apical (luminal) membrane, whereas MRP1 and MRP6 are localized on the basolateral membrane [129]. Moreover, P-gp, MRP2, MRP4, and MRP6 are expressed in renal proximal tubules, whereas MRP1 is localized in distal tubules and collecting ducts [129], protecting distal part of the nephron from toxic drug accumulation which may occur with water reabsorption. BCRP protein expression in kidney has been recently evidenced, with also a localization in proximal tubules [23] but its role in renal drug efflux remains to be clearly determined.

Beside their role in drug elimination, MDR transporters may also exert a protective role on the kidneys themselves, as these organs are particularly exposed to toxic compounds. In patients (or animals) with chronic renal failure, it has been observed that the renal expression of P-gp [130] or of Mrp2 [131] is increased while that of uptake transporters is decreased. This may help the sick organ to eliminate toxins. Modifications of the expression of MDR transporters may also contribute to modulate drug nephrotoxicity. It has been shown for example that the expression level of P-gp is lower in kidney graft recipients treated with ciclosporin A than in those treated with tacrolimus. This is correlated with a longer graft survival in the tacrolimus patients, attributed to a higher nephrotoxicity in the ciclosporin A group [132]. Overexpression of several MDR transporters (P-gp, Mrp2, Mrp4, Mrp5 [133]) and down regulation of influx transporters (OAT and OCT) has also been evidenced in mice treated with cisplatin, another nephrotoxic drug, even if its transport is not documented for all of them (see Table **2**).

MDR EFFLUX PUMPS AND TRANSPORTER-MEDIATED DRUG-DRUG INTERACTIONS

Polymedication is very frequent in clinical practice, especially in the elderly. It is often the cause of iatrogenic adverse reactions related either to drug-drug interactions or to inappropriate dosing due to organ insufficiency in old patients. Some mechanisms of pharmacokinetic interactions are now quite well characterized, like those mediated by the administration of inhibitors or inducers of cytochromes P450 or the formation of complexes between cationic and anionic compounds. Yet, it now appears that MDR transporters can also play a major role in drug –drug interactions. The most popular example is probably that of flavonoids present in grapefruit juice, which can inhibit both the P-gp-mediated efflux and the CYP3A4-mediated metabolism of many drugs in enterocytes, improving thereby their bioavailability [134, 135]. There is considerable overlap between CYP3A4 and P-glycoprotein substrates [136], so that both systems will often be involved in drug interactions, resulting in complex pharmacokinetic profiles of multidrug regimens [137]. As compared to CYP-mediated drug interactions, those mediated by MDR transporters have however the particularity of possibly affecting drug concentration in a specific body compartment (such as the brain) without modifying blood levels.

Drug-drug interactions related to MDR transporters can occur by two main mechanisms. The first one is a competition between drugs (substrates or modulators of the pump) for the binding site(s) of the transporter, which can impair the transport of one or the two interacting drugs. The second is a change in the expression level of the MDR transporter upon exposure to a given drug, but which can affect the transport of any other drug substrate of the same pump. These interactions are not always deleterious, one drug being able to boost the absorption of the second one. This is well exemplified in Kaletra®, which consists of the combination of a therapeutic dose of lopinavir and a low

dose of ritonavir, which only serve for inhibiting lopinavir efflux and metabolism, hence increasing its bioavailability [138-140].

Competition for Drug Binding Site

A combination of an efflux pump substrate with a well-characterized inhibitor/modulator can be useful to increase intestinal absorption or penetration into specific tissues, but it can also lead to adverse effects by decreasing drug elimination. On the other hand, the co-administration of two drugs substrates for the same transporter may sometimes result in unexpected and/or unwanted effects. One may anticipate that the drug with the highest affinity will be more efficiently transported, and thus inhibit the transport of the other drug. Yet, if the mechanism of the interaction is competitive, the concentration ratio between the two drugs may also play a critical role in determining which one will influence the transporter of the other one. Moreover, other mechanisms of interaction than simple competition for transport have been described, for example, allosteric modification by binding to a modulator site (see for example diclofenac, which inhibits the transport of anionic substrates by MRP2 [141] but stimulates that of amphiphilic substrates [142]). On these bases, it is clear that transporter-mediated drug interactions are not easy to predict *in vivo*, and are often understood *a posteriori.* Methods to accurately predict such interactions are therefore needed [96].

A series of drugs, which were first documented as being P-gp substrates, are now widely used both *in vitro* and *in vivo* for their modulator activity (among others, quinine and quinidine, verapamil, ciclosporin A and nifedipine; they constitute the first generation of P-gp modulators [143, 144]). Using P-gp knockout mice, Fromm *et al.* [145] showed that co-administration of quinidine increases digoxin concentrations in plasma and brain (by 73.0% and 73.2%, respectively) of wild-type mice, but not in *Mdr1a* (-/-) mice, demonstrating that quinidine is not only a substrate, but also a potent inhibitor of P-gp. In accordance with these results, a study with human volunteers showed that digoxin intestinal absorption increased from 22.3 ± 8.9% to 55.8 ± 21.2% of the dose when co-administrated with quinidine [90]. Digoxin oral bioavailability is also increased when co-administrated with talinolol [146], with a 23% increase of the area under the concentration-time curve AUC(0-72h), or clarithromycin [147] (1.7-fold increase in AUC(0-24h)), whereas its renal elimination is reduced when co-administrated with verapamil [148]. In another study with healthy male volunteers, quinidine caused an increase of loperamide transport into the brain, leading to several side effects, although the blood plasma concentration of loperamide remained unchanged [149].

Ciclosporin A, another well-known P-gp substrate [100], is also able to act as an inhibitor, increasing taxane (paclitaxel or docetaxel) oral bioavailability in wild-type mice [150] (from 9.3% up to 67% when co-administrated with ciclosporin A) as well as in cancer patients [151, 152] (from 4-8% for taxane alone, up to 47% or 88%, depending on the taxane, in presence of ciclosporin A). Similarly, the increased bioavailability and reduced clearance of the BCRP substrate irinotecan in patients treated concomitantly with ciclosporin A [153, 154] has been attributed to the inhibition of BCRP by ciclosporin A [155]. The clinical efficacy of ciclosporin A as a pump modulator is thus related to its ability to inhibit different MDR transporters (P-gp, BCRP, MRP1 [156]).

Anti-HIV therapy requires the combination of three or four antiretroviral drugs from different classes. Many anti-HIV drugs have been demonstrated as being substrates for MDR transporters, mainly P-gp and MRP2 (see Table **2**). However, ritonavir also behaves as a P-gp inhibitor and decreases digoxin clearance by 35%, in humans, likely because both drugs compete with P-gp for renal elimination [157]. P-gp and CYP3A4 inhibition by ritonavir or other protease inhibitors has also been evoked to explain the increased blood concentrations of tacrolimus [158], fexofenadine [159] or loperamide [160]. This could apply to much more classes of drugs that are substrates of both P-gp and CYP 3A4 [161]. Moreover, protease inhibitors are also inhibitors (but not substrates) of BCRP [162, 163], and could therefore also affect the pharmacokinetic profile of drugs that are substrates of this transporter. The same reasoning could apply to antifungal agents, which are substrates of P-gp but inhibitors of BCRP [164].

Several drug-drug interactions have been reported with the antifolate drug methotrexate. Co-administration of benzimidazole proton-pump inhibitors significantly inhibits BCRP-mediated transport of methotrexate *in vitro*, and pantoprazole reduces its clearance *in vivo* in mice (1.9-fold), possibly via competition for BCRP [165]. Co-administration of nonsteroidal anti-inflammatory drugs (NSAIDs) [166] also modifies methotrexate pharmacokinetics, possibly by inhibiting its renal tubular secretion via MRP2 and MRP4 [141, 167]; *in vitro* diclofenac inhibits BCRP-mediated methotrexate transport [142].

Much more interactions have been described in cellular or *in vitro* models. For example, bromocriptin increases L-dopa cellular accumulation about 2.05-fold in a rat brain endothelial cell model by inhibiting P-gp [168], whereas amiodarone inhibits digoxin secretion through P-gp in kidney epithelial cells [169]. Interactions with anticancer drugs have also been demonstrated. The antibiotics ofloxacin and erythromycin enhance vincristine accumulation in MRP1-overexpressing cells [170], and opiates (methadone and morphine) inhibit paclitaxel uptake by P-gp in human placental inside-out vesicles [171]. On the contrary, transport of paclitaxel, docetaxel, and saquinavir in MDCK cells overexpressing MRP2 is stimulated by diclofenac [142]. Further investigations are needed however to determine whether these are relevant in the clinics, as concentrations used *in vitro* are often supratherapeutic.

Drug-induced Change in Expression of MDR ABC Transporters

Regulation of transporters expression has been mainly studied in the liver, a key organ for drug detoxification and disposition (for comprehensive reviews, see [172, 173]). Several nuclear receptors like the pregnane X receptor (PXR, also referred as the steroid and xenobiotic receptor SXR), constitutive androstane receptor (CAR), peroxisome proliferator activated receptor alpha (PPARα), or nuclear factor-E2-related factor (Nrf2) are implicated in the induction by

xenobiotics of ABC transporters (P-gp, MRP2 [174], MRP3 [175], Mrp4 [176] or BCRP [177]), as well as of cytochromes P450 [178] or of uptake transporters (OATP) [179], enabling a coordinated response to drug injury. Nuclear receptors regulate target gene transcription in a ligand-dependent manner. Ligand binding promotes their activation and translocation to the nucleus, where they form homo- or heterodimers that bind to specific response elements within regulatory regions of the target gene. Several drugs are able to bind to and activate nuclear receptors, such as rifampicin, clotrimazole, phenobarbital, dexamethasone, nifedipine, or midazolam [180], and therefore to modulate MDR transporter expression (see Table **3**) [178, 181]. *In vitro*, other drugs induce rather gene amplification [182].

Rifampicin is known for a long time as an inducer of P-gp and MRP2 [183, 184], through a PXR-activation mechanism [185]. In human healthy volunteers, rifampicin treatment increases intestinal P-gp level, thus affecting oral bioavailability of several drugs, such as digoxin [184], talinolol [186], fexofenadine [187] or ciclosporin A [188]. Mice expressing human PXR and treated with rifampicin were also much less susceptible to methadone antinociceptive effect, demonstrating the increase of P-gp activity at the BBB after rifampicin treatment [189].

HIV protease inhibitors like amprenavir and nelfinavir [190], ritonavir [191, 192] or atazanavir [193] can induce intestinal P-gp overexpression in animals and in cultured cells [194, 195], through binding and activation of PXR, at clinically-relevant concentrations for ritonavir [196]. Ritonavir also induces MRP1 overexpression *in vitro* [191]. However, patients treated with protease inhibitors do not exhibit an increase in P-gp expression in lymphocytes, as compared to patients treated with other classes of antiretrovirals [197]. Yet, non-nucleoside and nucleoside reverse transcriptase inhibitors also induce intestinal P-gp expression *in vitro* probably via a PXR pathway [198, 199], making the previous study difficult to interpret.

In rats, repeated administration of oxycodone (an opioid agonist used for the management of pain in cancer patients) causes P-gp overexpression (in liver, kidney, and brain), and affects tissue concentration of paclitaxel [200]. Celecoxib, a NSAID, induces an increase in MRP4 and MRP5 expression *in vitro* at clinically relevant concentrations [201]. This could explain the lack of improvement in response rate observed in clinical trials examining celecoxib combined with irinotecan for solid malignancies [202]. Carbamazepine, an antiepileptic drug known as a CYP3A4 inducer, has been shown to induce both intestinal P-gp and MRP2 in human healthy volunteers, which affects talinolol pharmacokinetics [203]. Other antiepileptic drugs, among which phenobarbital (a known PXR activator), also increase P-gp, MRP1 and MRP2 expression levels after long-term exposure of rat brain microvascular endothelial cells [204, 205] as well as in rat brain [206]. This effect is associated with an activation of PXR and CAR receptors [205].

Acquired MDR phenotype in cancer cells often results from the overexpression of ABC transporters able to expel anticancer drugs out from the cells [10, 42]. This suggests that anticancer drugs can induce the expression of the corresponding transporter. Thus, resistant cell lines obtained *in vitro* after chronic exposure to various anticancer agents (see Table **3**) do indeed overexpress ABC transporters. The same strategy could be applied to other drug substrates, provided they can exert a certain toxicity on cells allowing to select those having acquired resistance. Successful examples include mouse macrophages exposed to ciprofloxacin, which overexpress Mrp4 [58, 207] or human erythroleukemia cells exposed to adefovir, which overexpress an indomethacin-sensitive efflux pump (later identified as being also MRP4) [208]. This strategy is thus very useful to obtain cells overexpressing efflux pumps as tools for molecular studies and characterization of drug transport [209]. The conditions needed to select cells *in vitro* are not relevant from the clinical situation (high concentrations; prolonged exposure), but clinical data suggests this also occurs during therapy. Induction of P-gp expression during treatment has been demonstrated for example in patients treated for bladder cancer with doxorubicin [210]. Overexpression of P-gp, MRPs or BCRP at the surface of cancer cells is frequently reported in tumors and constitute a poor prognosis factor [211, 212]. Interestingly also, these transporters show higher expression levels at the BBB in drug refractory epilepsy [213, 214].

MDR ABC TRANSPORTERS AS A DRUG TARGET

Considerable effort has been made over the last decade to develop efflux pump inhibitors as a way to improve efficacy of anticancer agents (see for recent reviews [215 and 216]). Yet, if *in vitro* or animal data are promising, success is limited in clinical trials, probably in relation with the pleiotropic character of the MDR transporters and with the difficulty of inhibiting transporters that have physiological roles without causing toxicity.

In a more general context, inhibition of apical transporters like P-gp and/or BCRP is also an attractive strategy to improve oral bioavailability and CNS penetration of drug substrates [103, 110, 120] but it may face the same limitations.

Another strategy could therefore rather consist of trying to select drugs that are poor substrates for efflux transporters. High throughput methods of *in vitro* and *in silico* screening should be helpful in this respect.

CONCLUSION

There is no doubt that active efflux transport should now be considered as a part of the evaluation of the pharmacokinetic profile of a drug, to the same extent as its metabolism by hepatic enzymes. Variations in the expression profile of transporters should also be considered with care to explain inter-individual variability.

The importance of characterizing transport by MDR efflux pumps is now recognized also by health authorities. In its last drug interaction guidance, the US Food and Drug Administration recommends indeed to test for transport, inhibition or induction of P-glycoprotein by new drugs, as a way to predict potential drug-drug interactions [217-219].

Table 3. Drug Inducers of MDR ABC Transporters Expression

ATC code		Pharmacological class	Drug	P-gp	MRP1	MRP2	MRP3	MRP4	MRP5	BCRP	Refs.
Cardiovascular system											
C	01A	Cardiac glycosides	Digoxin	+ (l)							[362]
	01B	Antiarrhythmics	Amiodarone	+ (s)							[181]
			Quinidine	+ (s)							[363]
	02A	Anti-hypertensive agents	Reserpine	+ (s)							[181]
	08C	Calcium channel blockers (vascular)	Nifedipine	+ (s)			+ (s)				[175, 181]
	08D	Calcium channel blockers (cardiac)	Verapamil	+ (s)							[181]
	10A	Lipid modifying agents	Atorvastatin	+ (s)							[363]
Genito-urinary system and sex hormones											
G	01A	Antiinfectives (triazole antifungal)	Clotrimazole	+ (s)			+ (s)				[175, 181]
Systemic hormons											
H	02A	Corticosteroids	Dexamethasone	**+** (r,s)		**+** (r,s) / - (s)	- (s)		- (s)	+ (r,s)	[364-366]
Anti-infectives											
J	01C	Beta-lactams	Flucloxacillin	+ (s)							[367]
	01F	Macrolides	Erythromycin	+ (s)							[181]
	01G	Aminoglycosides	Gentamicin			**+** (r,l)					[368]
	01M	Fluoroquinolones	Ciprofloxacin			+ (m,l)		+ (m,l)			[58]
	04A	Antimycobacterial antibiotics	Rifampicin	**+** (s,l)	+ (p,l) / - (s)	+ (s,l)	+ (s)		+ (s)	+ (s)	[175, 183-185, 366, 369-371]
	05A	Reverse transcriptase inhibitors	Zidovudine (AZT)	+ (l)				+ (l)	+ (l)		[41]
		Protease inhibitors	Atazanavir	+ (s)							[193]
			Nelfinavir	**+** (r,l)							[190]
			Ritonavir	+ (s), **+** (r,s)	+ (s)						[191, 192]
		Non-nucleoside reverse transcriptase inhibitors	Delavirdine	+ (s)							[198]
		-	Neviradine	+ (s)							[199]
Antineoplastic and immunomodulating agents											
L	01C	Plant alkaloids	Docetaxel	+ (s)							[372]
			Paclitaxel	+ (s)							[372]
			Vinblastine	+ (s)	+ (s)	- (s)					[366, 372]
			Vincristine	+ (s)		+ (s)	+ (s)				[369, 372]
	01D	Cytotoxic antibiotics	Doxorubicin	+ (s), **+** (l)	- (s)	- (s)			+ (s)	+ (m,l)	[68, 210, 366, 373, 374]
			Mitoxantrone	+ (s)						+ (l)	[182, 375, 376]
	01X	Camptothecins	Topotecan	+ (s)						+ (l)	[328, 363]
		Platinium compounds	Cisplatin	+ (p,s)	- (s)	+ (s)	+ (s)		**+** (s,l)		[366, 377-379]
		Protein kinase inhibitors	Imatinib	+ (l)	- (l)	- (l)				+ (l)	[380]
	02B	Hormon antagonists	Tamoxifen	+ (s)	- (s)	**+** (mo,l) / - (s)	- (s)		- (s)		[366, 372, 381]
	04A	Immunosuppressants	Sirolimus	+ (s)							[181]
			Tacrolimus	+ (s)							[181]

(Table 3) Contd .....

ATC code		Pharmacological class	Drug	P-gp	MRP1	MRP2	MRP3	MRP4	MRP5	BCRP	Refs.
Musculo-skeletal system											
M	01A	Anti-inflammatory agents	Celecoxib		- (s)	- (s)		+ (s)	+ (s)		[201]
Brain and nervous system											
N	02A	Opioid analgesics	Morphine	**+** (r,l)	**+** (r,l)					**+** (r,l)	[382, 383]
			Oxycodone	**+** (r,l)							[200]
	03A	Antiepileptics	Carbamazepine	**+** (l)		**+** (l)					[203]
			Phenobarbital	+ (s)	-	+ (s)				+ (s)	[174, 181, 366, 370]
	04B	Antiparkinsonian drugs	Bromocriptine	+ (m, s)							[384]
	05C	Hypnotics and sedatives	Midazolam	+ (s)							[181]
Antiparasitic products and insecticides											
P	01B	Antimalarials	Artemisinin	+ (s)							[385]

Drugs are classified according to ATC codes (Anatomical Therapeutic Chemical classification system; http://www.whocc.no/atc/).
Induction has usually been demonstrated *in vitro* (at mRNA and/or protein levels); symbols in bold correspond to *in vivo* induction. Studies were performed in animals: m, mouse; r, rat; p, pig; mo, rhesus monkeys; or in humans/human cell lines (no indication). Induction has been performed for short time (s) (≤ 72h), or long time (l) (> 3 days) periods.

Appropriate models are therefore critically needed to evaluate drug transport by specific efflux pumps. P-gp role is now appropriately evaluated, using reliable *in vitro* and *in vivo* procedures. Interactions caused by other MDR transporters still need to be examined on a case-by-case basis, as standard procedures are lacking. Furthermore, we also need filling the gap between *in vitro* and *in vivo* data to accurately predict the role of MDR efflux pumps in drug transport and drug interactions.

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